SYNOPSIS
SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL FUSED PYRIMIDINE AND THIAZINE HETEROCYCLES

SHORT RESUME OF THE PLAN PROPOSED FOR INVESTIGATION FOR Ph.D. DEGREE UNDER THE FACULTY OF SCIENCE

To be submitted to
SWAMI RAMANAND TEERTH MARATHAWADA UNIVERSITY, NANDED

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Thesis Title

Synthesis, Characterization and Biological Evaluation of some Novel Fused pyrimidine and thiazine Heterocycles.

- **Introduction:**

In recent years, the synthesis of fused bicyclic heterocyclic compounds possessing an pyrimido-thiazine & Pyrimido-pyrimidine central core has been the focus of great interest. This type of compounds shows various biological properties such as antibacterial, antiallergic, anti-inflammatory, antitumor, phsphodiesterase inhibition and ant Parkinsonism, many workers have synthesized different 1, 3-thiazines. Thiazines are very useful units in the fields of medicinal and pharmaceutical chemistry and have been reported to exhibit a variety of biological activities.

In recently substituted thiazine is prepared using different chalcones and that are very versatile substrates for the evolution of various reactions and physiologically active compounds. The reaction of thiourea with chalcone (Michael acceptor) results in 1, 3- thiazine and reaction of chalcone with guanidine results in 1, 3-pyrimidines. It has been well focused that the presence of pyrimido-thiazine and pyrimido-pyrimidine with various chemically reactive moieties is an important structural feature and also substituted imino and Oxo group present in thiazine and pyrimidine ring, and the resulting molecule would exhibit promising biological activities. In continuation of our work. In this work our plan to synthesize, pyrimido-thiazine and pyrimido-pyrimidine containing more reactive functional groups for further cyclisation and derivatization. The synthesized compounds reacting with various nucleophiles such as substituted aromatic amines, aromatic phenol, various active methylene compound and alicyclic heterocyclic compound construct pyrimido-pyrimidine and pyrimido-thiazine derivatives.

- **LITERATURE SURVEY:**

- Salimon Jumat et.al. reported synthesis of imidazole[1,2-a]pyridine-3 (2H)-one, 3-Phenylimidazo[1,2-a]pyridine and 3-bipheny-1-4-ylimidazo[1,2 a]pyridine, from 2-aminopyridine which reacts with chloroacetic acid, phenyl acetyl chloride and 4-phenyphenacyl bromide, in ethanol respectively.

- Elnagdi M.H. et.al. Reported the preparation of pyrido [4,3-d] pyrimidine's alternatively, treating of 5-cyano-6-cyanomethyl, pyrimidine's with sulfuric acid.

- Nagaraj et.al. synthesize Bis[3[(E)-3-(4-substituted-phenyl)-3-oxo-1-propenyl]4-hydroxy-phenyl] methane on treating with thiourea followed by cyclization in ethanolic KOH produces bis- thiazine derivatives

- Glotova et.al. Synthesize 1-Acyl-2-bromoacetylene derivatives when treated with thiourea in the presence of glacial acetic acid produce α-oxoketene mercaptals. The latter in $BF_3.Et_2O$, with the removal of cyanamide and water undergoes intramolecular cyclization to give 1,3- thiazine-6-thione hydrobromide which on recrystallization with water-alcohol yields pure substituted 2-amino-1,3-thiazine-6-thiones

- **Objectives:**
  - Specific objectives of our current research program include the synthesis of Novel pyrimido-pyrimidine and pyrimido-thiazine and their derivatives.
  - One pot synthesis of amino pyrimidine and amino thiazine
  - Reaction of amino pyrimidine and amino thiazine nucleus with Michael acceptor to give pyrimido-pyrimidine and pyrimido-thiazine.
  - Reaction of pyrimido-pyrimidine and pyrimido-thiazine nucleus with various aromatic phenols.
  - Reaction of pyrimido-pyrimidine and pyrimido-thiazine nucleus with various aromatic amines.
  - Reaction of pyrimido-pyrimidine and pyrimido-thiazine nucleus with various Heteryl amines.
  - Reaction of pyrimido-pyrimidine and pyrimido-thiazine nucleus with various Benzothiazole.
  - Biological activity of above synthesized compounds.

- **Methodology:**
  - By known three component system synthesis of amino pyrimidine and amino thiazine.
  - The synthesized amino pyrimidine and amino thiazine is act as a Michael donor and it nucleophilically condense with Michael accepter to give pyrimido- pyrimidine and pyrimido- thiazine.
  - Pyrimido-pyrimidine and pyrimido-thiazine act as electrophilic species condense with various nucleophile such as aromatic amines, aromatic phenols, hetryl amines etc.
  - Biological evaluation of above synthesized compounds

- **International status :**

Since from the last three decades, we have witnessed the revolutionary synthesis Pyrimido pyrimidine and pyrimido thiazine of many researchers throughout the World. Although there are huge number of articles on pyrimido pyrimidine and Pyrimido thiazine.

1. Pecorari P, Rinaldi M, etal Synthesis and biological activity of pyrimido [2,1-b] [1,3]thiazine, [1,3]thiazino[3,2-a]purine and [1,2,3]triazolo[4,5-d] [1,3]thiazino[3,2-a] pyrimidine derivatives and thiazole analogues.
2. Covington R.R; Temple D.L., YevichJ.P. (1982) "Antial- lergics: 3-(1H-tetrazol-5-yl) - 4H-pyrimido [2, 1- b] ben-zothi- azol-4-ones," Journal of Medicinal Chemistry, Vol. 25, No. 7, pp. 864-868.
3. Wade JJ, Toso CB, Matson CJ, Stelzer VL (1983) Synthesis and antiallergic activity of some acidic derivatives of 4H-pyrimido[2,1-b]benzazol-4-ones. J Med Chem 26: 608-611

- **National Status :**

Apart from the international contribution some of the Indian researchers have also made their mark on synthesis of pyrimido pyrimidine and pyrimido thiazine.

In this section some of the research groups can be mentioned like

1. V. Sundari G. Nagarajan S. Gurumurthy and R. Valliappan (2009), synthesis characterization and biological activities of 3, 5-Diaryltetrahydro-N-[(phenyl amino) methyl]-1, 4-thiazine-1, 1-dioxide.
2. Vachala S. Dinakaran, Bhargavi Bomma and keloth K. srinivasan (2012) synthesized fused pyrimidine the heterocycles of diverse biological and pharmacological significance.

- **Regional status:**

1. Sambhaji P. vartale, Vijay N.Bhosale, Sandeep V. Khansole and ramdas N. Katapalle (2009). A convenient one pot synthesis of 3-cyno-9-methyl-2-methylthio-4-oxo-4H-pyrimidi-[2, 1-b] [4, 5-b] quinoline and its reaction with selected nucleophiles. Letters in organic chemistry Vol.6, No7, 544-548.
2. Baheti KG and Kuberkar SV "Synthesis and biological activity of 4H-pyrimido [2, 1-b] benzothiazole-8-substituted-2-thiomethyl-3-cyano-4-ones." (2003) Ind J Het Chem 12: 343D.
3. Baheti KG, Jadhav JS, Suryawanshi AT and Kuberkar SV (2005) Novel synthesis and antibacterial activity of 15-iminobenzothiazole[2,3b] pyrimido [5,6e] pyrimido[2,3]benzothiazole-14-H ones and its 3,10 disubstituted derivatives. Ind J Chem 44B: 834D
4. Pingle MS, Vartale SP, Bhosale VN and Kuberkar SV (2006) A convenient synthesis of 3-cyano-4-imino-2- methylthio-*4H*pyrimido [2, 1-*b*] [1, 3] benzothiazoles and its reactions with selected nucleophilesArkivoc X, 190D.
5. Vartale SP, Jadhav JS, Kale MA and Kuberkar SV (2006) Synthesis and antimicrobial activity of 6/7/8- substituted-1-[aryl/6'-substituted-2'-benzothiazolyl]-pyrazolo [4, 5-b] quinolines Ind J Chem.

- **Scope of the study :**

A lot of research work is going on all over the world to investigate organic compounds which will act as effective medicines as anti-HIV, anti-Cancer and anti-tuberculostatic drug Antibacterial. National Institutes of Health, National Cancer Institute, Bethesda, Maryland, USA showed keen interest in evaluation of compounds, identified in our earlier research publications for anti-HIV and anti-cancer screening. It is surmised that some newly synthesized compounds mentioned in our proposal would exhibit properties required for effective drugs. Synthesis and screening of newly synthesized compounds would lead to the formation of pharmacological important compounds as a good antibacterial.

Proposed work plan with tentative chapter scheme.

Year	Quarters (Periods of three months)	Milestones
Year I	1 st Quarter	Reference Work
	2 nd Quarter	Topic first literature survey
	3rd Quarter	Topic second Experimental Work and characterization
	4th Quarter	Topic second Experimental Work and characterization
Year II	1 st Quarter	Topic third Experimental Work and
	2 nd Quarter	Topic third Experimental Work and characterization
	3rd Quarter	Topic Fourth Experimental Work and characterization
	4th Quarter	. Topic Fourth Experimental Work and characterization
Year III .	1 st Quarter	Topic Fifth Experimental Work and characterization
	2 nd Quarter	Topic sixth Biological evaluation
	3rd Quarter	Topic sixth Biological evaluation
	4th Quarter	Writing and typing of the research work and submission of the research work

Expected Outcome

It is planned to synthesize newly designed compounds which are free from toxic effects and possess good biological activity.

References:

- Gupta S, Ajmera N, Gautam N, Sharma R and Gautam DC (2009) ChemInform Abstract: Novel Synthesis and Biological Activity Study of Pyrimido[2,1-b]benzothiazoles. Ind J Chem 48B: 853.
- Dash B. Patra M. and Mahapatra P.K. Synthesis of thiazolo pyrimidine derivatives,*J.Inst.Chem*.52[2],**1980**,92.
- Glennon RA, Gaines JJ, Rogers ME (1981) Benz-fused mesoionic xanthine analogues as inhibitors of cyclic-AMP phosphodiesterase. J Med Chem 24: 766-769.
- Covington R.R;Temple D.L.,YevichJ.P. (1982) “Antial- lergics: 3-(1H-tetrazol-5-yl)-4H-pyrimido[2,1- b] ben-zothi- azol-4-ones,” Journal of Medicinal Chemistry, Vol. 25, No. 7, , pp. 864-868.
- Wade JJ, Toso CB, Matson CJ, Stelzer VL (1983) Synthesis and antiallergic activity of some acidic derivatives of 4H-pyrimido[2,1-b]benzazol-4-ones. J Med Chem 26: 608-611.
- Chincholkar MM and Ramekar MA (1994) “Synthesis of Some New 4,6-Diaryl-5-aroyl-2-imino-6H-2,3- dihydro- 1,3- thiazines”.J Ind Chem Soc 71: 199.
- Raut AW etal (2001) “ Synthesis of Schiff bases of thiophene-2-carboxaldehyde and its antimicrobial activity” Orient J Chem. 2001;17:131–3.
- Rajesh Vyas, Prakash Choudhary, Hariom Sharma and Varma BL (2008) “ Microwave-assisted synthesis of 6H- 2-amino-4,6- diaryl-1,3-thiazines” Indian J Heterocyclic Chem 17: 237.

- Jhala YS, Pradhuman, Ranawat S, Dulawat SS and Varma BL (2005) “Microwave assisted synthesis of chalcones using Claisen-Schmidt condensation in dry media Indian J Heterocyclic Chem 14: 357.
- Kelly DR, Caroff E, Flood RW, Heal W, Roberts SM (2004) The isomerisation of (Z)-3-[2H1]-phenylprop-2- enone as a measure of the rate of hydroperoxide addition in Weitz-Scheffer and Julia-Colonna epoxidations. Chem Commun (Camb) : 2016-2017.
- Iwata S, Nishino T, Inoue H, Nagata N, Satomi Y, et al. (1997) Antitumorigenic activities of chalcones (II). Photo-isomerization of chalcones and the correlation with their biological activities. Biol Pharm Bull 20: 1266-1270.
- Jain AC and Prasad AK (1995) Reaction of chalcone 2-4,-dimethoxychalcone, a-bromo and methoxy chalcone with thiourea Indian J Chem 34B: 496.
- Sambhaji P. vartale, Vijay N.Bhosale , Sandeep V. Khansole and ramdas N. Katapalle (2009) . A convenient one pot synthesis of 3-cyno-9-methyl-2-methylthio-4-oxo-4H-pyrimidi-[2,1-b][4,5-b]quinoline and its reaction with selected nucleophiles. Letters in organic chemistry Vol.6,No7,544-548.
- Galabov AS, Galabov BS, Neykova NA (1980) Structure-activity relationship of diphenylthiourea antivirals. J Med Chem 23: 1048-1051.
- Baheti KG, Kapratwar SB and Kuberkar SV (2002) A convenient synthesis of 2,3 disubstituted derivatives of 4H-pyrimido [2,1-b]benzotjiazole-4-one Synth Comm 32: 2237
- Baheti KG and Kuberkar SV (2003) Novel Synthesis of 3-Amino-4-oxo-(2*H*)-pyrazolo[3',4':4,5]pyrimido- [2,1- *b*]benzothiazole and its 2- and 3-Substituted Derivatives J Het Chem 40: 547.
- Baheti KG and Kuberkar SV “Synthesis and biological activity of 4H-pyrimido [2,1-b] benzothiazole-8- substituted-2-thiomethyl-3-cyano-4-ones.” (2003) Ind J Het Chem 12: 343.

- Baheti KG, Jadhav JS, Suryawanshi AT and Kuberkar SV (2005) Novel synthesis and antibacterial activity of 15-iminobenzothiazole[2,3b] pyrimido [5,6e]pyrimido[2,3]benzothiazole-14-H ones and its 3,10 disubstituted derivatives. Ind J Chem 44B: 834.
- Pingle MS, Vartale SP, Bhosale VN and Kuberkar SV (2006) A convenient synthesis of 3-cyano-4-imino-2-methylthio-*4H*pyrimido [2, 1-*b*] [1,3] benzothiazoles and its reactions with selected nucleophilesArkivoc X, 190.

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